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Brief communication

Lutetium-177–prostate-specific membrane antigen ligand following radium-223 treatment in men with bone-metastatic castration-resistant prostate cancer: real-world clinical experience

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Disclaimer

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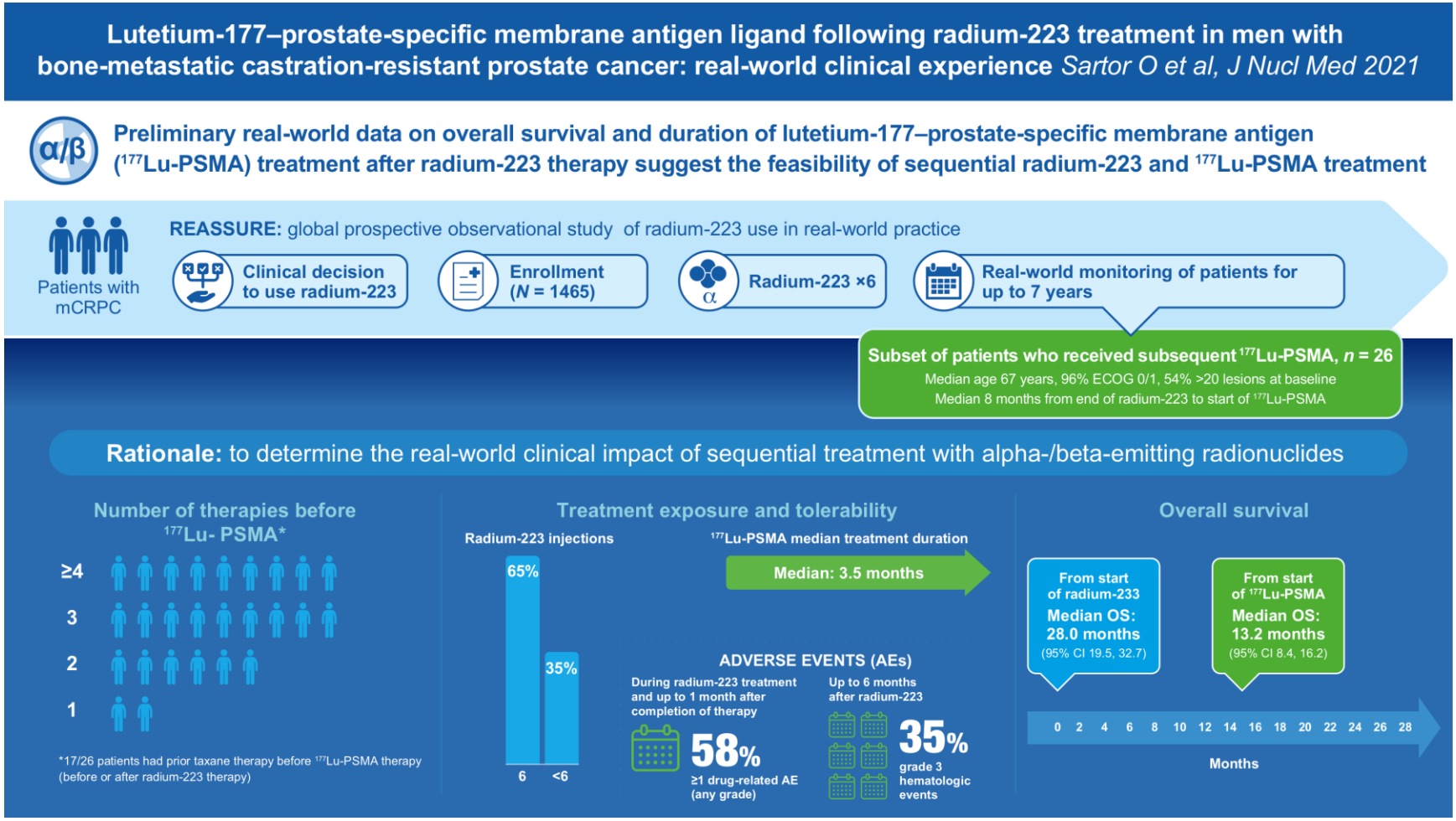
^{177}Lu-PSMA after radium-223 in mCRPC

ABSTRACT

We analyzed real-world clinical outcomes of sequential alpha-/beta-emitter therapy for metastatic castration-resistant prostate cancer (mCRPC). **Methods:** We assessed safety and overall survival in 26 patients who received lutetium-177–prostate-specific membrane antigen ligand (^{177}Lu-PSMA) following radium-223 in the ongoing non-interventional Radium-223 alpha Emitter Agent Safety Study in mCRPC popUlation for long-teRm Evaluation (REASSURE; NCT02141438). **Results:** Patients received radium-223 for a median 6 injections and subsequent ^{177}Lu-PSMA for a median 3.5 months (≥4th therapy in 69%). The median time between radium-223 and ^{177}Lu-PSMA treatment was 8 months (range 1–31). Grade 3 hematologic events occurred in 9/26 patients (during or after ^{177}Lu-PSMA treatment in 5/9 patients; 8/9 patients had also received docetaxel). Median overall survival was 28.0 months from radium-223 start and 13.2 months from ^{177}Lu-PSMA start. **Conclusion:** Although the small sample size precludes definitive conclusions, these preliminary data, especially ^{177}Lu-PSMA treatment duration, suggest feasibility of ^{177}Lu-PSMA use after radium-223 in this real-world setting.

Key Words: ^{177}Lu–prostate-specific membrane antigen; metastatic castration-resistant prostate cancer; radium-223; real-world evidence; treatment sequence

Graphical Abstract



PLAIN LANGUAGE SUMMARY

REASSURE is a study of men with metastatic castration-resistant prostate cancer who are given targeted radiotherapy with radium-223 as part of their normal treatment (that is, not in a clinical trial). Within this study, 26 men have been treated with radium-223 and then a different kind of targeted radiotherapy, named lutetium-177–prostate-specific membrane antigen ligand (^{177}Lu-PSMA for short). We wanted to know how these two different radiotherapy treatments used one after another would affect patients. Most patients received the full course of radium-223 treatment (6 injections) and at least half of the participants received ^{177}Lu-PSMA for more than 3 months. Nearly three quarters of the patients had already received three or more other drugs before they were given ^{177}Lu-PSMA; from this information, we can tell that most patients had very advanced disease. Among the 26 patients that we studied, at least half were alive more than 2 years after starting radium-223 treatment and more than 1 year after starting treatment with ^{177}Lu-PSMA. Although we cannot draw definite conclusions from this very small number of patients, and therefore we need to do more research, we believe that it may be feasible to use ^{177}Lu-PSMA after radium-223 in some patients with advanced prostate cancer, because the men in our study appeared to be able to tolerate ^{177}Lu-PSMA treatment for several months, and many of them were still alive more than a year later, even though they had very advanced disease.

INTRODUCTION

The alpha-emitter radium-223 demonstrated significantly prolonged overall survival and a favorable safety profile versus placebo in men with metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 ALSYMPCA trial *(1)*. Lutetium-177–prostate-specific membrane antigen ligand (^{177}Lu-PSMA) is an investigational beta-emitting radioligand with accumulating evidence of clinical efficacy and acceptable toxicity in men with advanced-stage mCRPC *(2–5)*.

Early experience in patients who have received both radium-223 and ^{177}Lu-PSMA indicates tolerable safety and therapeutic response with this sequence (*6–8*). We sought to add to the evidence base on sequential alpha/beta-emitting therapy, using data from participants in an ongoing, global, prospective, observational study of radium-223 who received subsequent ^{177}Lu-PSMA.

MATERIALS AND METHODS

Patients with mCRPC involving bone scheduled to receive radium-223 in clinical practice were included in REASSURE (Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation; NCT02141438). Primary outcomes included short-term and long-term safety. Methods and results from a previous interim analysis have been reported *(9)*. This paper is based on the second prespecified interim analysis (data cut-off: March 20, 2019).

Disease characteristics, adverse events following radium-223 treatment, and overall survival are described for patients who received the experimental drug ^{177}Lu-PSMA in compassionate-use or investigational settings after radium-223. Treatment-emergent serious adverse events and drug-related adverse events were recorded during radium-223 treatment or up to 30 days after the last radium-223 dose. Grade 3/4 hematologic adverse events were

systematically collected up to 6 months after radium-223; neutropenic fever and/or hemorrhage were recorded in patients with subsequent chemotherapy up to 6 months after the last dose of chemotherapy. Drug-related serious adverse events continued to be recorded until end of follow-up (maximum 7 years). Adverse events during and after ^{177}Lu-PSMA therapy were not systematically recorded unless they met the above criteria.

The study conduct complied with the requirements of the European Medicines Agency, the US Food and Drug Administration, applicable local laws and regulations, and International Conference on Harmonization – Good Clinical Practice guidance. Participants provided written informed consent, and ethics committee or institutional review board approvals were obtained according to local laws in participating countries.

RESULTS

Twenty-six patients in the USA, Germany, Austria, Italy, and Israel received ^{177}Lu-PSMA after radium-223. Their median age was 67 years, 96% (25/26) had an Eastern Cooperative Oncology Group performance status of 0 or 1, and 54% (13/24 with baseline scans) had more than 20 lesions at baseline (Table 1).

Before starting radium-223, 85% of patients (22/26) received ≥1 life-prolonging systemic anticancer therapy (Supplemental Figure 1), including androgen receptor-targeted therapy (enzalutamide and/or abiraterone acetate) in 65% (17/26) and docetaxel in 42% (11/26).

Before starting ^{177}Lu-PSMA, 92% of patients (24/26) had received ≥2 life-prolonging therapies, 69% (18/26) had received ≥3 therapies, and 8% (2/26) had received only radium-223; 65% (17/26) received prior docetaxel, and 8% (2/26) also received cabazitaxel between radium-223 and ^{177}Lu-PSMA treatment; 50% (13/26) had no other life-prolonging treatment between radium-223 and ^{177}Lu-PSMA (Figure 1, Supplemental Figure 1).

The median number of radium-223 injections was 6 (range 1–6); 17/26 patients (65%) received 6 injections. The median time from end of radium-223 to start of ^{177}Lu-PSMA treatment was 8 months (range 1–31; Figure 2). The median duration of ^{177}Lu-PSMA treatment was 3.5 months (range 0.5–21.2; Figure 2).

Fifteen patients (58%) experienced treatment-emergent drug-related adverse events during radium-223 treatment (Table 2). Nine patients (35%) had grade 3 hematologic toxicities (Table 3); 8/9 patients had previously received docetaxel, before (*n*=5) or after (*n*=3) radium-223 therapy; 2/9 patients had also received cabazitaxel after radium-223. The hematologic toxicities developed during or after ^{177}Lu-PSMA treatment in 5 patients (6 events). No grade 4 hematologic events were recorded.

Median overall survival was 28.0 months (95% confidence interval 19.5, 32.7) from the start of radium-223 therapy and 13.2 months (8.4, 16.2) from the start of ^{177}Lu-PSMA therapy.

DISCUSSION

Although ^{177}Lu-PSMA is not yet approved for patients with mCRPC, patients are increasingly receiving this investigational treatment in clinical trials or compassionate-use programs. Most patients receive ^{177}Lu-PSMA after multiple prior systemic anticancer therapies, including radium-223 in some cases, as recorded in the REASSURE study. This subgroup analysis of REASSURE, which reflects real-world clinical practice, adds to the evidence for the feasibility of sequential radium-223 and ^{177}Lu-PSMA treatment, with a median overall survival of >1 year from the start of ^{177}Lu-PSMA therapy. Only 3 patients had serious adverse events related to radium-223, and the reported (albeit incompletely) incidence of grade 3 hematologic events was acceptable, mostly consisting of anemia, which may be partially explained by increasing disease burden. Furthermore, the treatment duration for ^{177}Lu-PSMA (median 3.5

months) indicates that several patients were able to receive multiple cycles, even though most patients had received ≥3 prior life-prolonging therapies, including taxane chemotherapy.

The 13-month median overall survival in our analysis is consistent with a retrospective multicenter study, in which median overall survival from start of ^{177}Lu-PSMA therapy was around 11 months in 85 patients with prior radium-223 (*7*) and 16.4 months in patients with 6–20 bone lesions treated with radium-223 and ^{177}Lu-PSMA (*10*). In another analysis, rates of grade 3 hematologic toxicity were low in patients with or without prior radium-223 therapy (anemia 1/20 [5%] vs 3/29 [10%]; thrombocytopenia 1/20 [5%] vs 2/29 [7%]) (*6*), which again supports our findings, although we did not systematically assess hematologic toxicity in all patients during ^{177}Lu-PSMA treatment, which we acknowledge as a limitation of our study.

Additional limitations are the small sample size, reflecting the experimental status of ^{177}Lu-PSMA, and the lack of a randomized control group. Because ^{177}Lu-PSMA is still an investigational agent, treatment was likely undertaken in academic settings (eg, university hospital cancer centers), so it is unknown whether the findings can be extrapolated to real-world community settings. The treatment duration and overall survival after ^{177}Lu-PSMA initiation indicate that its use after radium-223 in heavily pretreated mCRPC patients is feasible, but interpretation is hindered by lack of a comparator arm, and possibly only the fittest patients were selected for ^{177}Lu-PSMA treatment. Nevertheless, this interim analysis of an ongoing real-world study provides clinically meaningful evidence in patients with mCRPC who successfully received sequential alpha/beta-emitting treatments.

CONCLUSION

In this real-world population of heavily pretreated patients with mCRPC, a treatment sequence of targeted alpha therapy with radium-223 followed by the beta emitter ^{177}Lu-PSMA

seemed feasible, based on the duration of ^{177}Lu-PSMA therapy, although definitive conclusions cannot be drawn.

Disclosure

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KEY POINTS

Question: Is it feasible to treat men with metastatic castration-resistant prostate cancer with sequential alpha- and beta-emitting therapies?

Pertinent findings: Subgroup analysis of a global observational study of radium-223 therapy indicated a low rate of serious adverse events and hematologic toxicities in patients who also received ^{177}Lu-PSMA, and many patients were able to receive multiple doses of ^{177}Lu-PSMA (a marker of tolerability). This sequence provides overall survival of >2 years from initiation of radium-223 and >1 year from initiation of ^{177}Lu-PMSA, even in heavily pretreated patients.

Implications for patient care: Sequential use of alpha and beta emitters appears to be feasible in selected patients, on the basis of the known safety profile of radium-223 and the duration of subsequent ^{177}Lu-PSMA; this sequence warrants further investigation.

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FIGURE 1. Anticancer therapies administered before lutetium-177–prostate-specific membrane antigen. All patients received radium-223.

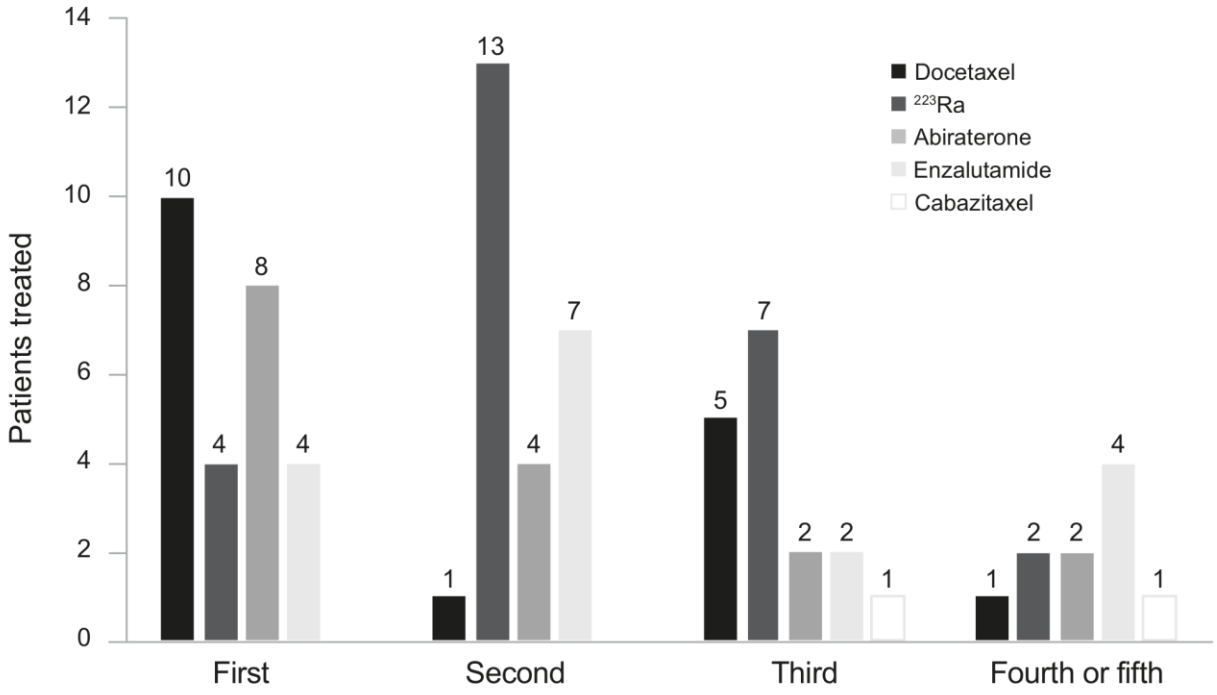

FIGURE 2. Time since end of radium-223 to start of lutetium-177–prostate-specific membrane antigen ligand (^{177}Lu-PSMA) and duration of ^{177}Lu-PSMA therapy.

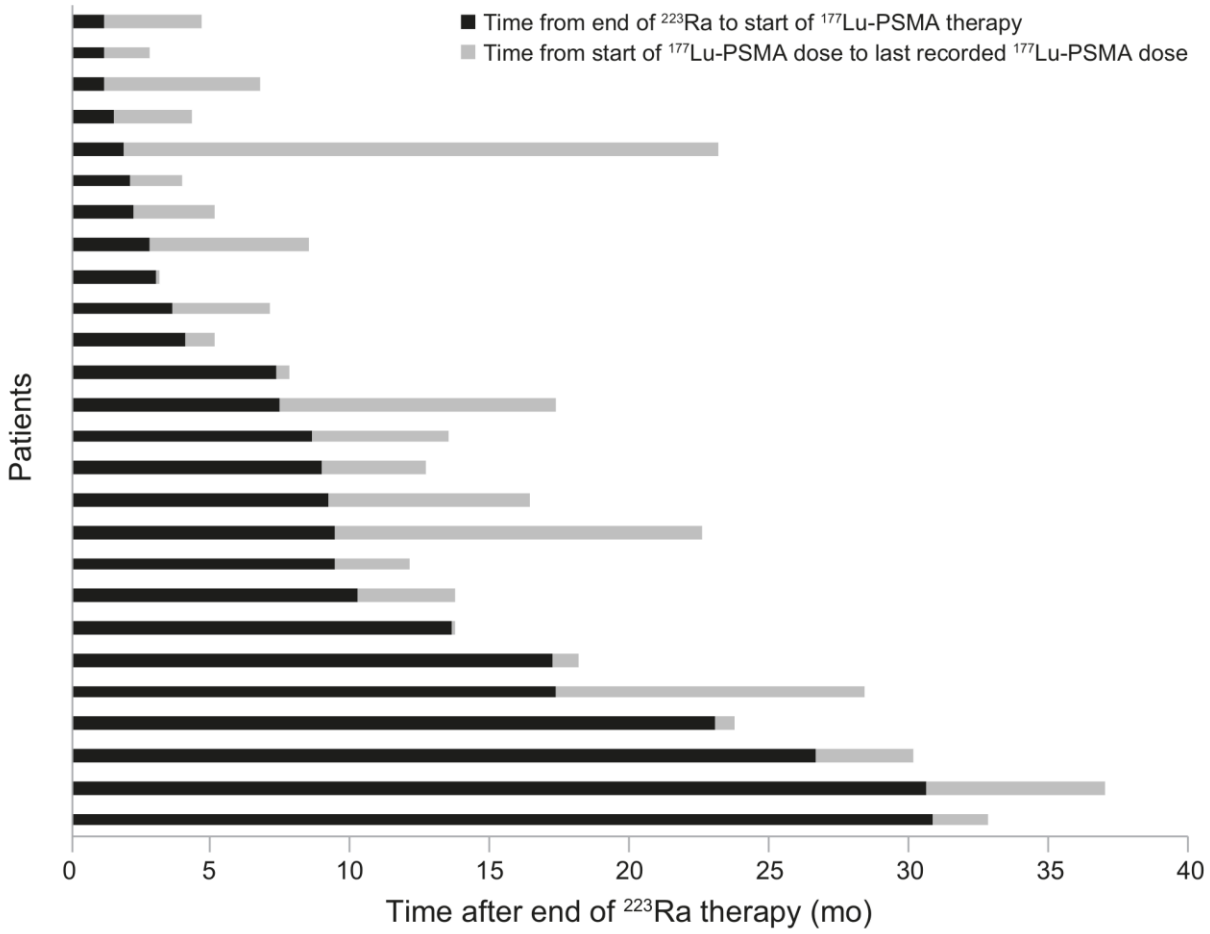

TABLE 1

Baseline Disease Characteristics

Timepoint	Characteristic		*N*=26
At initial diagnosis	Gleason score, n (%)	≤6	3 (12)
		7	9 (35)
		8–10	12 (46)
		Unknown	2 (8)
	Stage (American Joint Committee on Cancer criteria), n (%)	Stage I	5 (19)
		Stage IIB	1 (4)
		Stage III	3 (12)
		Stage IV	13 (50)
		Missing	4 (15)
At start of radium-223 therapy	Time from diagnosis of castration-resistant prostate cancer, median (range), months		20 (6–48)
	Time from diagnosis of bone metastases, median (range), months		23 (3–40)
	Extent of disease, n (%)*	<6 lesions	2 (8)
		6–20 lesions	7 (29)
		>20 lesions	11 (46)
		Superscan	2 (8)
		Missing	2 (8)
	Primary tumor status, n (%)	Unresected	11 (42)
		Resected, status of residual tumor unknown	3 (12)
		R0 complete resection, all margins histologically negative	6 (23)
		R1 incomplete resection, microscopic margin involvement	5 (19)
		Missing	1 (4)
	Laboratory values, median (range)	Prostate-specific antigen, ng/mL (*n*=21)	127 (8–1,319)
		Alkaline phosphatase, U/L (*n*=20)	147 (45–769)
		Lactate dehydrogenase, U/L (*n*=14)	228 (112–393)
		Hemoglobin, g/dL (*n*=23)	13 (9–15)

*Baseline scan data available for 24/26 patients.

TABLE 2

Adverse Events During and After Radium-223 Treatment

Adverse events	Incidence, n (%)
Drug-related	
Treatment-emergent*	15 (58)
Serious†	3 (12)
Bone-associated events	6 (23)
Fractures	2 (8)
Bone disorders‡	4 (15)

N=26.

*During radium-223 therapy and up to 30 days after last radium-223 dose.

†During radium-223 therapy and up to 7 years after last radium-223 dose.

‡Excluding congenital disorders and fractures, according to Medical Dictionary for Regulatory Activities version 21.1.

TABLE 3

Grade 3 Hematologic Adverse Events*

Patients with events, n (%)†	After start of radium-223 therapy		
	Overall	**Starting before ^{177}Lu-PSMA treatment**	**Starting during or after ^{177}Lu-PSMA treatment‡**
Any	9 (35)	5 (19)	5 (19)
Leukopenia	0	0	0
Neutropenia	0	0	0
Pancytopenia	1 (4)	0	1 (4)
Thrombocytopenia	3 (12)	2 (8)	1 (4)
Anemia	6 (23)	3 (12)	4 (15)

N=26.

*No grade ≥4 events were recorded.

†Patients may have had >1 event at different times; these patients are counted only once in the Any row and Overall column.

†Grade 3/4 hematologic toxicity data were systematically recorded only up to 6 months after completion of radium-223 therapy; data are therefore not consistently available for patients who received ^{177}Lu-PSMA after this window.

SUPPLEMENTAL FIGURE 1. Sequence of anticancer therapies administered before lutetium-177–prostate-specific membrane antigen (177Lu-PSMA) treatment. All patients received radium-223.